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Anticoagulation: a practical guide for strabismus surgeons

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Summary

An increasing number of surgical strabismus patients are taking oral anticoagulant and antiplatelet agents, with more diverse mechanisms of action than those used in the past. The decision as to whether to continue these drugs throughout the perioperative period is difficult and must be based on the balance between hemorrhagic and thrombotic risk. To help guide strabismus surgeons with clinical management in these cases, we review potential hemorrhagic complications of strabismus surgery and examine the use of anticoagulant and antiplatelet drugs during the perioperative period. Surgical strategies that might help minimize intraoperative hemorrhage in patients on anticoagulant therapy are also discussed.

Ophthalmologists are increasingly likely to encounter patients on anticoagulation and antiplatelet therapy (ACAPT). The frequency of adult strabismus surgery has increased by up to 24% over the past 15 years, with a peak incidence in the 8th decade of life.[1,2] This adult population has shown a steady rise in the use of anticoagulation therapy, with a 38% increase in the use of oral anticoagulation between 2009 and 2014 in the United States.[3] Approximately half of these patients are on the newer non-vitamin K oral anticoagulants, such as dabigatran and rivaroxaban, which were introduced in 2010. Similarly, there was a 57% increase in the regular use of aspirin between 2005 and 2010.[4]

Therefore, surgeons can expect an increasing number of strabismus patients to be on ACAPT, underscoring the need to understand how these medications affect surgical planning. We review the hemorrhagic complications of strabismus surgery and provide an update on existing antiplatelet and anticoagulant agents to lay groundwork for managing strabismus patients on ACAPT.

Potential Hemorrhagic Complications of Strabismus Surgery

Most published guidelines examining the perioperative management of anticoagulation categorize ocular surgery as low hemorrhagic risk, but they rarely separate strabismus surgeries from other ophthalmic procedures. While the risk of vision-threatening hemorrhage in strabismus surgery is extremely low, hemorrhagic complications can cause significant morbidity. Thus, careful surgical planning is required to prevent complications.

One of the most devastating complications of strabismus surgery is retrobulbar hemorrhage. There are case reports of retrobulbar hematomas occurring in anticoagulated patients undergoing regional anesthesia, including peribulbar, retrobulbar, and sub-Tenon's blocks.[5] Large-scale studies are divided on whether there is an increased risk of visually

significant hematomas in these patients, probably because of the rarity of this complication.[6-8] Although the risk is low, the consequences are vision threatening, and surgeons should consider alternatives to regional anesthesia in anticoagulated patients.

Retrobulbar hemorrhage associated with strabismus surgery without regional anesthesia has also been reported. Carden and colleagues[9] published a case of bilateral retrobulbar hemorrhage during routine bilateral strabismus surgery under general anesthesia; the patient was later discovered to be using high-dose garlic supplements, which have antiplatelet activity and may have contributed to the hemorrhage. Arès and Superstein[10] reported a case of spontaneous retrobulbar hemorrhage 2 days after strabismus surgery, presenting as an infected hematoma and orbital cellulitis. Todd and colleagues[11] described a retrobulbar hemorrhage 36 hours after surgery triggered by coughing and straining. Surgeons should be vigilant for any signs of orbital compartment syndrome and be prepared to perform a lateral canthotomy and cantholysis. Bleeding complications not only threaten vision but may also cause muscle slippage requiring surgical reexploration and repair.[12]

Other hemorrhagic complications can affect patient comfort and perception of surgical outcomes. Eyelid hemorrhages, which can occur independently of regional blocks, can cause discomfort and patient distress due to appearance. These hemorrhages are more common after surgery on the inferior oblique muscle. In addition to the disturbing appearance, subconjunctival hemorrhages can also cause corneal dellen, placing the patient at risk of corneal perforation if not appropriately managed.

The effect of anticoagulation on surgical outcomes has been studied in cataract, vitreoretinal, oculoplastics, and glaucoma surgeries,[13-16] but the effect on strabismus surgery has been little studied. Kemp and colleagues[17] published a case series of 3 patients successfully

undergoing strabismus surgery while taking warfarin, without complications. However, Coats and Olitsky[18] reported that patients on anticoagulation are more likely to require cautery for hemostasis during strabismus surgery (14.8% vs 1.2%), suggesting that these patients have more intraoperative bleeding. Thus, an understanding of available antiplatelet and anticoagulant drugs is important in order to strike a safe balance between hemorrhagic and thrombotic risks.

Antiplatelet Agents

Aspirin (Acetylsalicylic acid, ASA)

ASA is widely used for the primary and secondary prevention of cardiovascular disease and has been found to decrease all-cause mortality, major cardiovascular events, and colorectal cancer.[19,20] Zhou and colleagues[4] estimates a 57% increase in regular aspirin use in the United States between 2005 to 2010. In addition, Stuntz and Bernstein[21] found that 30% of adults over the age of 40 take aspirin on a regular basis.

Aspirin suppresses the production of prostaglandins and thromboxane by irreversibly inhibiting cyclooxygenase. The loss of thromboxane in platelets leads to decreased affinity for platelet aggregation for the lifetime of the platelet. The antiplatelet effect, which is responsible for the cardiovascular benefit of regular aspirin use, also makes intraoperative hemostasis more challenging.

Because aspirin functions as a nonreversible inhibitor, the duration of the antiplatelet effect depends on the rate of platelet turnover. Platelets exposed to aspirin will be inhibited, but platelets made after aspirin dosing will not be affected. It has been suggested that patients discontinue aspirin 3 days prior to planned surgery, because hemostasis is normalized if 20% of platelets have normal cyclooxygenase activity, and 12% of circulating platelets are replaced every 24 hours.[22,23] One study in healthy volunteers showed complete normalization of platelet

function and bleeding times by 6 days after aspirin cessation in 100% of study subjects, independent of dosing.[24] Thus, if platelet normalization is required for surgery, stopping aspirin at least 5-7 days prior to surgery is recommended.

Patients with recent coronary artery angioplasty or stent placement are at particularly high risk of thrombotic complications and myocardial infarction during the perioperative period because of increased risk of thrombosis and discontinuation of antiplatelet medications.[25,26] Current guidelines suggest delaying elective noncardiac surgery for 14 days after coronary artery balloon angioplasty, 30 days after bare metal stent implantation, and 1 year after drug-eluting stent implantation if antiplatelet agents need to be discontinued for the procedure.[27] Some have suggested that with the newer generation of drug-eluting stents, delaying elective surgery for 180 days is sufficient to lower the risk to the baseline.[27]

The benefit of aspirin as primary prevention in nonstented patients is uncertain, and guidelines suggest that initiation or continuation of aspirin is not beneficial in patients undergoing elective noncardiac noncarotid surgery.[28]

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Commonly used for analgesia, NSAIDs function similarly to aspirin via cyclooxygenase inhibition. However, in contrast to aspirin, their inhibitory action is reversible, which leads to a decreased duration of antiplatelet effect. Normalization of platelet function depends on the half-life of the particular NSAID used: ibuprofen has a half-life of approximately 2 hours, whereas naproxen has a half-life of 17 hours.

Gobble and colleagues[29] examined the use of ketorolac postoperatively in a range of nonophthalmic surgeries, and found no evidence to suggest an increase in postoperative bleeding. In uncomplicated cases, ketorolac and other NSAIDS may be used safely for

postoperative pain, but in complex cases, or those with several risk factors, other analgesic agents should be considered. Topical NSAIDs may be effective as a postsurgical analgesic and can be used as an alternative to systemic administration.[30]

ADP/P2Y12 Inhibitors

As a class, adenosine diphosphate (ADP) receptor inhibitors, including clopidogrel, prasugrel, ticlodipine, and ticagrelor, are most commonly used in the acute setting for myocardial infarction. These drugs can also be used in patients who cannot tolerate aspirin, since they have similar prophylactic efficacy for cardiovascular protection. In patients who have undergone coronary stenting, ADP inhibitors are frequently used in combination with aspirin for a dual antiplatelet effect to minimize the risk of stent thrombosis.

The antiplatelet effect of these drugs is mediated by the inhibition of P2Y12 subtype of ADP receptors on platelet cell membranes, which is critical for platelet aggregation. Like aspirin, clopidogrel, prasugrel, and ticlodipine have irreversible inhibition; therefore, restoration of normal platelet function in these patients depends on the rate of platelet turnover. Ticagrelor inhibition is reversible, with a half-life of about 8 hours, and, along with prasugrel, it is thought to have greater clinical efficacy than clopidogrel. If normal platelet function is desired for surgery, recent guidelines suggest a 5-day abstinence period for clopidogrel, ticlodipine, and ticagrelor, and 7 days for prasugrel.[31]

Anticoagulant Agents

Heparin

Heparin, a naturally occurring anticoagulant that binds to and activates antithrombin III, which then inactivates thrombin and factor Xa in the coagulation cascade, is available as unfractionated heparin (UNF) and low-molecular weight heparins (LMWH). It is frequently used to treat

myocardial infarction and is also used in the management of atrial fibrillation, pulmonary emboli, and venous thromboembolisms. Heparin is not absorbed orally and must be administered parenterally, either subcutaneously or intravenously.

Due to the short half-life of heparin, normalization of hemostatic ability occurs within hours of last administration, usually 1-2 hours for UNF and within 5-6 hours for LMWH. Protamine sulfate may be used for more rapid reversal of UNF heparin action.

Warfarin

Warfarin inhibits vitamin-K dependent synthesis of clotting factors II, VII, IX, X and proteins C and S.[32] In medical use since 1954, it is frequently used for the treatment of pulmonary emboli and deep venous thrombosis and is also used for thromboembolic prophylaxis in atrial fibrillation and prosthetic heart valve implantation.

Warfarin dosing is patient dependent and requires laboratory monitoring to titrate the correct dosage. Prothrombin time, and the derived international normalized ratio (INR), are used to assess a patient's coagulative function. The target INR for most patients lies between 2.0 and 3.0, although prosthetic heart valve patients require a higher anticoagulation goal of 2.5-3.5.

Warfarin's half-life is approximately 36-42 hours; thus, normalization of INR may take 5 days. However, this depends on initial INR and the patient's ability to synthesize clotting factors. The American College of Chest Physicians recommends a target INR of <1.5 for most surgical procedures, although the recommendation does not specifically discuss strabismus surgery.[33] Administration of vitamin K accelerates normalization of hemostatic ability by augmenting natural synthesis of clotting factors. More rapid reversal of warfarin activity, as may be required in massive hemorrhage, requires the transfusion of fresh frozen plasma, which contains the downregulated clotting factors.

Because of the amount of time needed to reach the target INR both when initiating and stopping warfarin therapy, there is concern for recurrent thromboembolism in high-risk patients. In addition, initiating warfarin therapy leads to a temporary state of hypercoagulability, which lasts approximately 3 days because of the more rapid downregulation of anticoagulant proteins C and S.[34] To mitigate this risk, patients may require heparin bridging in the perioperative transitional period.

Patients being discontinued from warfarin are stratified based on their risk of thromboembolism. It is recommended that patients at low risk for thromboembolism not use a heparin bridge.[33] For patients at high risk for thromboembolism, warfarin is discontinued 5 days before the surgical procedure and heparin is started to prevent thrombotic complications of inadequate anticoagulation. Historically this was accomplished at the hospital once the INR is below 2.0 for initiation of intravenous UNH. Heparin was administered until 4-6 hours before the surgical procedure. Following the procedure, with hemostasis and low risk of bleeding, heparin could be restarted. Generally, it was recommended that warfarin be restarted12-24 hours after hemostasis, although, because there is no reversal agent for warfarin, some chose to delay restarting warfarin in select cases. The patient remained in the hospital until the INR is >2.0, at which point the heparin can be discontinued.

The development of LMWH has allowed outpatient management of a heparin bridge.[33] It is recommended that LMWH be stopped 24 hours before the procedure. Other important, but often overlooked, aspects of perioperative heparin bridging include providing a patient calendar for stopping and starting anticoagulation medications, patient education for the administration of LMWH, rechecking INR levels before surgery to ensure a return to baseline, and discussion of risks/benefits of heparin bridging.

Direct Thrombin Inhibitors

This drug class disrupts the anticoagulation cascade by way of factor II (thrombin) inhibition and includes dabigatran, bivalirudin, argatroban, and desirudin. Of these, only dabigatran is available in an oral form and is thus the most likely to be encountered by strabismus surgeons. Dabigatran, introduced in 2010, has evolving clinical indications and the benefit of more rapid onset and no need for therapeutic monitoring, while having a similar safety profile as warfarin.[35,36]

Like other anticoagulants, dabigatran is most frequently used in the management of venous thromboembolism, atrial fibrillation, and, less commonly, for acute coronary syndrome. Because it is eliminated by the kidneys, the duration of anticoagulation activity depends on the individual's renal function. If there is low hemorrhagic risk in a patient with normal creatinine clearance, dabigatran can be discontinued 24-48 hours prior to surgery.[37] In patients with impaired renal clearance (CrCl <50), or for patients with high hemorrhagic risk, it should be discontinued 3-5 days prior to surgery.

Rapid reversal in an emergent or life-threatening setting can be accomplished by administration of idarucizumab. Dabigatran reaches peak anticoagulant effect within 2-3 hours of administration, so there is no need for heparin bridging when resuming therapy. This drug can be restarted within 24 hours for procedures with low hemorrhagic risk and 48-72 hours for high-risk procedures.

Direct Factor Xa Inhibitors

The direct factor Xa inhibitors, which first became available in 2011, include rivaroxaban, apixaban, and edoxaban and are approved for use for atrial fibrillation and venous thromboembolism. Along with dabigatran, they are often referred to under the umbrella term "novel oral anticoagulants" or "non-vitamin K anticoagulants" (NOACs). Like dabigatran, this

class also benefits from an onset of action within 1-4 hours and no need for laboratory monitoring. If preoperative confirmation of residual anticoagulant affect is desired, factor Xa levels can be drawn.

These medications are cleared through the kidneys, with half-lives typically ranging between 5-12 hours. If planning to discontinue anticoagulation in patients with normal creatinine clearance and low thromboembolic risk, rivaroxaban and apixaban can be discontinued 24-48 hours preoperatively, and edoxaban can be discontinued 72 hours prior. These medications should be stopped earlier in patients with decreased creatinine clearance, depending on the degree of renal impairment. The bleeding risk profile is favorable for these medications compared to warfarin.[38] For rapid reversal of anticoagulation, andexanet alfa is a recombinant protein that has been recently approved for use by the Food and Drug Administration.[39]

Herbal Supplements

St John's wort, ginkgo biloba, garlic, and ginseng have varying levels of antiplatelet and anticoagulant effects, which are most notable in patients already on antithrombotic medications. Carden and colleagues[9] document bilateral retrobulbar hemorrhage during routine bilateral lateral rectus recession in a patient taking large quantities of garlic extract. Fong and colleagues[40] reported a case of retrobulbar hemorrhage after retrobulbar anesthesia in a patient on gingko biloba. In both cases, the patients did not inform their surgeons about their herbal supplementation, which demonstrates how easily these alternative medicines may be overlooked by both patients and providers. In practice, it is impossible to make concrete recommendations on whether to postpone surgery when patients take these supplements. Cases should be evaluated on risk and individual histories.

Managing Anticoagulants and Antiplatelet Agents in the Perioperative Period

The decision on whether and for how long to discontinue antithrombotic agents depends on balancing hemorrhagic and thrombotic risk. This assessment should be made in coordination with the patient's primary care provider or cardiologist to best determine the degree of risk associated with anticoagulation cessation. Once the risk has been determined, a decision can be made about how best to manage the patient's antiplatelet or anticoagulant drugs during the perioperative period (Figure 1).

Determining Hemorrhagic Risk

The patient's medical issues should be carefully considered in the assessment of perioperative hemorrhagic risk. Several coexisting diseases can exacerbate the problem. Uncontrolled hypertension can make intraoperative hemorrhage difficult to control. Patients with impaired renal and hepatic function may have an inherent coagulopathy, and impaired anticoagulant clearance may require earlier preoperative medication discontinuation or monitoring of coagulability prior to surgery (Table 1). Chronic alcohol use also impairs coagulation by affecting platelet function and factor synthesis. Obtaining an accurate history of personal and family of bleeding will aid in uncovering conditions such as hemophilia, von Willenbrand factor deficiency, or Glanzmann's thrombasthenia, which can significantly increase hemorrhagic risk. Intraoperative factors can also affect the degree of surgical hemorrhage. The risk increases with more complex procedures or with reoperations because of prolonged operative time and increased surgical disruption of underlying anatomy. The type of anesthesia can also affect hemorrhagic risk. While regional anesthesia can result in retrobulbar hemorrhage, general anesthesia can lead to coughing and bucking during extubation and bleeding at the surgical site.

Determining Thrombotic Risk

Both the European Society of Cardiology and the American Heart Association/American College

of Cardiology/Heart Rhythm Society recommend using the CHA_2DS_2-VASC score to stratify atrial fibrillation patients as high, medium, or low risk for thromboembolism.[41,42,27] According to these guidelines, patients with prosthetic mitral valves, recent strokes or transient ischemic attacks, recent thromboembolism, or a history of thrombophilia have a >10% annual risk for thromboembolic events. Interruption of anticoagulation for strabismus surgery should be carefully assessed for these patients. If in discussion with the patients' physicians, cessation of therapy is agreed upon, then heparin bridging will be required to minimize perioperative risk. In contrast, low-risk patients do not need bridging therapy (Table 2).

Patients on antiplatelet therapy can be similarly stratified on risk. Aspirin can be safely discontinued in patients without a history of myocardial infarction or stroke. In contrast, a trial by Oscarsson and colleagues[43] found that high-risk patients benefit from continuation of perioperative antiplatelet therapy. This study demonstrated that continuation of aspirin in the perioperative period in patients with a history of ischemic heart disease, congestive heart failure, renal impairment, stroke or transient ischemic attack, or insulin-dependent diabetes significantly decreased the rate of cardiovascular events (1.8% vs 9.0% [$P = 0.02$]).

For patients with recent coronary stenting, the risk of stent thrombosis appears to be greatest within the first 6 weeks of placement for bare-metal stents and within the first 6 months for drug-eluting stents (ACCP guidelines). Since dual antiplatelet therapy should be continued without interruption during this time, ophthalmologists should consider delaying strabismus surgery until the patient is outside this window.

Analgesia Considerations

Strabismus surgery requires minimal postoperative analgesia. Local analgesia in combination with acetaminophen and occasionally low-dose opioids is usually sufficient. Ketorolac, and

intravenous NSAIDs, can impair platelet function and may increase postoperative bleeding. In patients who are at high risk for bleeding, ketorolac should not be used in the peri-operative period. Since strabismus surgery is inherently nauseating, opioids should be used sparingly. Intravenous acetaminophen is a good choice for analgesia in patients who are unable to tolerate oral medications, and in whom ketorolac is contraindicated.

Local Control of Hemostasis During Surgery

Agents with alpha-agonist activity, such as epinephrine and oxymetazoline, can be applied topically to induce vasoconstriction and decrease intraoperative hemorrhage. These agents can be placed directly onto the eye after surgical field preparation, so the effect of vasoconstriction is working as the surgeon makes the first incision. When using epinephrine as the vasoconstricting agent, a concentration of 1:10,000 (100 mcg/ml) should be used for routine cases and of 1:1,000 (1000 mcg/ml) for cases with greater hemostatic concern. Although the risk of cardiovascular effects is minimal with topically applied epinephrine, tachycardia and hypertension can occur. In patients in whom these effects would have negative consequences, discussion with the anesthesia provider prior to administration will be helpful.

Careful surgical technique can help minimize surgical bleeding even in the setting of anticoagulant and antiplatelet therapy. Identification of conjunctival and ciliary vessels is crucial, so the surgeon can avoid or gently cauterize these vessels. Cautery may be used early in the surgery during muscle isolation and suture placement to avoid bleeding. Cautery prior to dissection of connective tissues with small vessels may also be helpful, and oxymetazoline-soaked cotton-tip applicators can be used for blunt dissection. Suturing the muscle deep to the vessels can help to avoid inadvertent nicking of the vessels.

Conclusions

The landscape of anticoagulant and antiplatelet therapies is rapidly evolving, with an increasing arsenal of drugs becoming available, accompanied by complex indications for use. As more surgical patients are taking these medications, it is important that the strabismus surgeon understand how to approach clinical care in these cases. Surgical hemorrhagic and thrombotic risks must be carefully balanced, and the timing of antithrombotic cessation should be individualized with the assistance of the patient's primary care physician, cardiologist, or neurologist.

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References

1. Astle AT, Foulsham T, Foss AJ, McGraw PV. Is the frequency of adult strabismus surgery increasing? Ophthalmic Physiol Opt 2016;36:487-93.
2. Martinez-Thompson JM, Diehl NN, Holmes JM, Mohney BG. Incidence, types, and lifetime risk of adult-onset strabismus. Ophthalmology 2014;121:877-82.
3. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. Am J Med 2015;128:1300-1305e5.
4. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. poulation. Pharmacoepidemiol Drug Saf 2014;23:43-50.
5. Subbiah S, McGimpsey S, Best RM. Retrobulbar hemorrhage after sub-Tenon's anesthesia. J Cataract Refract Surg 2007;33:1651-2.
6. Kallio H, Paloheimo M, Maunuksela EL. Haemorrhage and risk factors associated with retrobulbar/peribulbar block: a prospective study in 1383 patients. Br J Anaesth 2000;85:708-11.
7. Benzimra JD, Johnston RL, Jaycock P, et al. The Cataract National Dataset electronic multicentre audit of 55 567 operations: antiplatelet and anticoagulant medications. Eye 2009;23:10-16.
8. Huebert I, Heinicke N, Kook D, et al. Dual platelet inhibition in cases of severe retrobulbar hemorrhage following retrobulbar and peribulbar anesthesia. J Cataract Refract Surg 2015;41:2092-101.
9. Carden SM, Good WV, Carden PA, Good RM. Garlic and the strabismus surgeon. Clin Exp Ophthalmol 2002;30:303-4.

10. Arès C, Superstein R. Retrobulbar hemorrhage following strabismus surgery. J AAPOS 2006;10:594-5.

11. Todd B, Sullivan TJ, Gole GA. Delayed orbital hemorrhage after routine strabismus surgery. Am J Ophthalmol 2001;131:818-19.

12. Cates CA, Hodgkins PR, Morris RJ. Slipped medial rectus muscle secondary to orbital hemorrhage following strabismus surgery. J Pediatr Ophthalmol Strabismus 2000;37:361-2.

13. Morris A, Elder MJ. Warfarin therapy and cataract surgery. Clin Exp Ophthalmol 2000;28:419-22.

14. Meillon C, Gabrielle PH, Bron AM, Creuzot-Garcher C. Antiplatelet and anticoagulant agents in vitreoretinal surgery: a prospective multicenter study involving 804 patients. Graefe's Arch Clin Exp Ophthalmol 2019;257:427.

15. Ing E, Douketis J. New oral anticoagulants and oculoplastic surgery. Can J Ophthalmol 2014;49:123-7.

16. Cobb CJ, Chakrabarti S, Chadha V, Sanders R. The effect of aspirin and warfarin therapy in trabeculectomy. Eye 2007;21:598-603.

17. Kemp PS, Larson SA, Drack A V. Strabismus surgery in patients receiving warfarin anticoagulation. J AAPOS 2014;18:84-6.

18. Coats DK, Olitsky SE. Strabismus surgery and its complications. Philipp M, Himberger M, eds. Berlin, Heidelberg: Springer-Verlag; 2007:318.

19. Guirguis-Blake JM, Evans C V., Senger CA, O'Connor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. preventive services task force. Ann Intern Med 2016;164:804-13.

20. Cuzick J, Thorat MA, Bosetti C, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol 2015;26:47-57.

21. Stuntz M, Bernstein B. Recent trends in the prevalence of low-dose aspirin use for primary and secondary prevention of cardiovascular disease in the United States, 2012-2015. Prev Med Reports 2017;5:183-6.

22. Patrono C, Ciabarroni G, Patrignani P, Pugliese F, Filabozzi P, Catella F, et al. Clinical pharmacology of platelet cyclooxygenase inhibition. Circulation 1985;72:1177-84.

23. O'Brien JR. Effect of the anti-inflammatory agents on platelets. Lancet 1968;291:894-5.

24. Cahill RA, McGreal GT, Crowe BH, et al. Duration of increased bleeding tendency after cessation of aspirin therapy. J Am Coll Surg 2005;200:564-73.

25. Berger PB, Kleiman NS, Pencina MJ, et al; EVENT Investigators. Frequency of major noncardiac surgery and subsequent adverse events in the year after drug-eluting stent placement: Results from the EVENT (evaluation of drug-eluting stents and ischemic events) registry. JACC Cardiovasc Interv 2010;3:920-27.

26. Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003;42:234-40.

27. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American college of cardiology/American heart association task force on practice guidelines. J Nucl Cardiol. 2015;22:162-215.

28. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014;370:1494-503.

29. Gobble RM, Hoang HLT, Kachniarz B, Orgill DP. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. Plast Reconstr Surg 2014;133:741-55.

30. Akyol-Salman I, Leçe-Sertöz D, Baykal O. Topical pranoprofen 0.1% is as effective anti-inflammatory and analgesic agent as diclofenac sodium 0.1% after strabismus surgery. J Ocul Pharmacol Ther 2007;23:280-83.

31. Godier A, Fontana P, Motte S, Steib A, Bonhomme F, Schlumberger S, et al. Management of antiplatelet therapy in patients undergoing elective invasive procedures: proposals from the French Working Group on perioperative hemostasis (GIHP) and the French Study Group on thrombosis and hemostasis (GFHT). In collaboration with the French Society for Anesthesia and Intensive Care (SFAR). Arch Cardiovasc Dis 2018;111:210-23.

32. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):160S-198S.

33. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(2 Suppl):e326S-e350S.

34. Grip L, Blombäck M, Schulman S. Hypercoagulable state and thromboembolism following warfarin withdrawal in post-myocardial-infarction patients. Eur Heart J 1991;12:1225-33.

35. Healey JS, Eikelboom J, Douketis J, et al; RE-LY Investigators. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the randomized evaluation of long-term anticoagulation therapy (RE-LY) randomized trial. Circulation 2012;126:343-8.

36. Schulman S, Carrier M, Lee AYY, et al; Periop Dabigatran Study Group. Perioperative management of dabigatran: a prospective cohort study. Circulation 2015;132:167-73.

37. Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103:1116-27.

38. Garcia D, Alexander JH, Wallentin L, et al. Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. Blood 2014;124:3692-8.

39. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;375:1131-41.

40. Fong KCS, Kinnear PE. Retrobulbar haemorrhage associated with chronic Gingko biloba ingestion. Postgrad Med J 2003;79:531-2.

41. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Rev Esp Cardiol (Engl Ed). 2017;70:50.

42. John Camm A, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2012;33:2719-47.

43. Oscarsson A, Gupta A, Fredrikson M, et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. Br J Anaesth 2010;104:305-

Legends

FIG 1. Suggested preoperative algorithm for optimizing hemorrhagic risk of the strabismus surgery process.

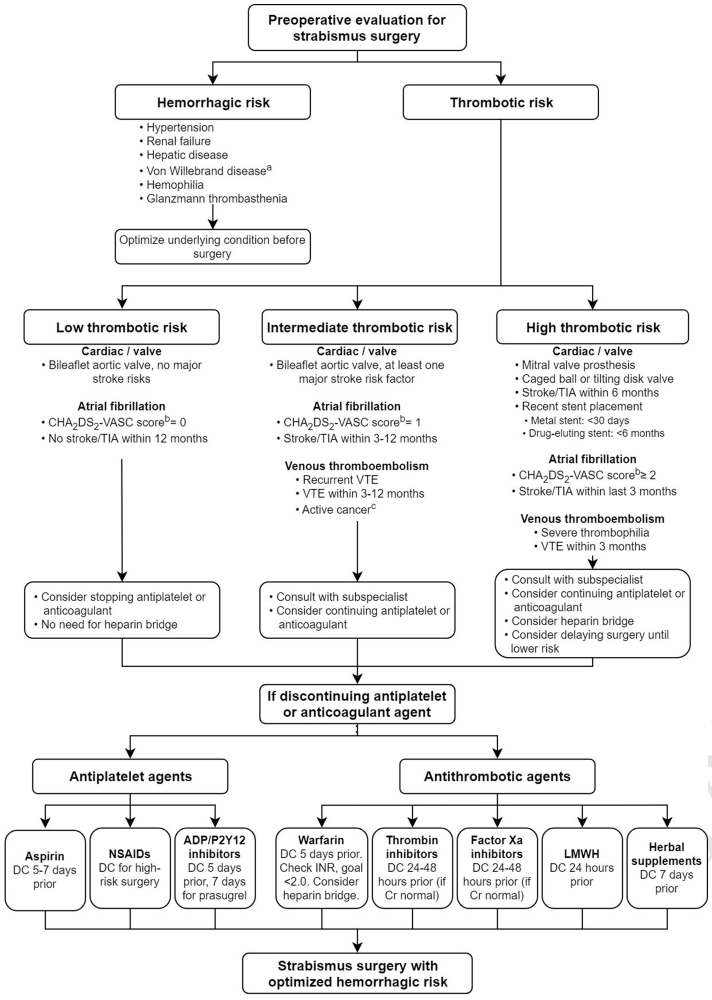
Table 1. Commonly used antiplatelet and anticoagulant drugs, half-lives, and route of drug clearance

Drug	Trade Name	Mechanism	Half-life	Clearance
Aspirin	—	Cyclooxygenase inhibitor	2-3 hours	Renal
Clopidogrel	Plavix	ADP/P2Y12 inhibitor	7-8 hours	Hepatic
Warfarin	Coumadin	Vitamin K antagonist	20-60 hours	Renal
Enoxaparin	Lovenox	Low molecular weight heparin	4.5 hours	Renal
Dabigatran	Pradaxa	Thrombin inhibitor	14-17 hours	Renal
Rivaroxaban	Xarelto	Factor Xa inhibitor	8-9 hours	Renal, fecal
Apixaban	Eliquis	Factor Xa inhibitor	7-8 hours	Renal, fecal

Table 2. Risk stratification for perioperative thromboembolism (Douketis and colleagues[33])

Risk	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High	• Any mitral valve prosthesis • Caged-ball or tilting disc aortic valve prosthesis • Stroke or TIA within 6 months	• $CHADS_2$ score of 5 or 6 • Rheumatic valvular heart disease • Stroke or TIA within 3 months	• VTE within 3 months • Severe thrombophilia (eg protein C/S deficiency, antiphospholipid antibodies)
Moderate	• Bileaflet aortic valve prosthesis and any major stroke risk factors	• $CHADS_2$ score of 3 or 4	• Recurrent VTE • VTE within 3-12 months
Low	• Bileaflet aortic valve prosthesis without any major stroke risk factors	• $CHADS_2$ score of 0-2 and no recent stroke or TIA	• Active cancer • VTE >12 months, no other risks

$CHADS_2$, congestive heart failure, hypertension, age>75 years, diabetes mellitus, stroke or transient ischemic attack; *TIA*, transient ischemic attack; *VTE*, venous thromboembolism.



[a]Consider administering 20u DDAVP before surgery.
[b]CHA_2DS_2-VASC score:
1 point for age 65-74, female sex, CHF, HTN, history of stroke or TIA, diabetes, prior MI, peripheral arterial disease or aortic plaque.
2 points for age >75 years (female sex cannot be the only point, but is additive with other risk factors).
[c]Active cancer may be intermediate or high risk depending on type of cancer.